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Prüfungsantrag gem. § 44 PatG ist gestellt

(54) Präparat zur Therapie und Prophylaxe von Erkrankungen, die bei Imbalancen von Plasmalipiden auftreten

(57) Das Präparat dient zur Therapie und Prophylaxe von Erkrankungen, die bei Imbalancen von Plasmalipiden auftreten. Als Wirkstoff ist eine Dosis Droloxifene enthalten.

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TI Droloxifene for therapy and prophylaxis of disorders characterized by imbalance in plasma lipids
IN Denecke, Rainer
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CC 1-10 (Pharmacology)
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PRAI	DE 1993-4304639	A1	19930216		
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CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
DE 4401554	ICM	A61K031-135
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	IPCR	A61K0009-52 [I,C*]; A61K0009-52 [I,A]; A61K0031-135 [I,C*]; A61K0031-135 [I,A]

AB Droloxifene and its salts and derivs. are useful for treatment of elevated plasma triglycerides, cholesterol, and lipoproteins, for treatment of **atherosclerosis**, and as a cardioprotectant.

ST droloxifene **hyperlipidemia atherosclerosis**

IT Anticholesteremics and Hypolipemics
(droloxifene for therapy and prophylaxis of disorders characterized by imbalance in plasma lipids)

IT Antiarteriosclerotics
(antiatherosclerotics, droloxifene for therapy and prophylaxis of disorders characterized by imbalance in plasma lipids)

IT **82413-20-5**, Droloxifene 82413-20-5D, Droloxifene, derivs. 97752-20-0, Droloxifene citrate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(droloxifene for therapy and prophylaxis of disorders characterized by imbalance in plasma lipids)

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Description of DE4401554	Print	Copy	Contact Us	Close

Result Page

The invention concerns a preparation to the therapy and prophylaxis of illnesses, which arise with Imbalancen of Plasmalipiden.

Such disease pictures arise for example, if to high blood fat values are present and thereby in particular the occurrence of Arteriosklerose is favoured. Important here arising effects become for example in the essay ?Biology OF Disease? Peter F. Davies, Laboratory Investigation, volume. 55, No. 1, page 5 FF., 1986, described. Measures for the lowering of critical parameters become oral in ?One Year Study OF Effects OF at Oestrogen dominance Contraceptive on serum High Density Lipoprotein Cholesterol, Apolipoproteins A-I and A-II and Hepatic Microsomal Function?, P.V. Luoma, J.E. Heikkinen, C. Ehnholm and P.R. Ylöstalo, European journal OF Clinical Pharmacology (1987), 31: 563-567, described. Further illnesses, which can be affected by Droloxifene preventively and therapeutically, are primary and secondary Hyperlipoproteinämien (Hypercholesterinämie, Hypertriglyceridämie and the mixed Hyperlipidämie) as well as disturbances of of the complex Lipide (Lipoide), z. B. Sphingolipidosen. Droloxifene lowers also the Fibrinogenplasmaspiegel, and has a mehrgleisige impact pronounced by therefore, which is not reached by other Antihyperlipidämika in the way. The Fibronogenerhöhung in the blood is to be regarded as independent cardiovascular factor of risk; thus it can be stated that Droloxifene exhibits different starting points distinguished in its kardioprotektive characteristics.

Also the so-called. ?broad beta disease?, which accompanies with strongly increased risk to the Artherosklerose, is for Droloxifene an indication area. Due to empirical observations it is further well-known that Hyperlipidämien affect the Endometriose syndrome of the woman negatively.

Here it concerns heterotopische Uterus mucous membrane plants in various fabrics those is functionally active and very heterogeneous disease pictures to thus induce can.

Those so far did not admit preparations are suitable however in sufficient way for ensuring with small side effects a high effectiveness with the indications application forms planned in each case.

Task of the available invention is it to indicate a preparation of the kind introductory specified in such a manner that a high effectiveness is reached when simultaneous reduction of side effects.

This task is solved according to invention by the fact that as active substance a dose Droloxifene is contained. The daily dose should amount to at least 0.1 mg/kg body weight, until therapeutic success medically aimed at eingetrete is. In preventive application the dose the individual requirements can be lowered accordingly.

The production of Droloxifene is described in the EP-OS 0,054,168. It essentially concerns with Droloxifene modified Tamoxifen, with which a hydroxyl group was changed concerning its positioning. An indication from Droloxifene to the treatment of bone diseases is in the EP-OS 0,509,317.

A further variation pharmakologischen when using Droloxifene becomes in ?Droloxifene, A new one anti- oestrogen in Postmenopausal Advanced Breast CAN cerium: Preliminary Results OF A double-blindly Dosefinding phase II Trial ", Peter F. Bruning, Eur J. CAN cerium, volume. 28A, No. 8/9, page 1404-1407, 1992, describe. Another use of the active substance Tamoxifen is in the essay to ?Antiestrogens. 3. Estrogen Receptor Affinities and Antiproliferative Effects in MCF-7 Cells OF Phenolic Analogues OF Trioxifene. . . ?, Charles D. Jones, Larry C. Blaszczak, Mary E. Goettel, Tulio Suarez, Thomas's A. Crowell, Thjomas E. Mabry, Peter C. Ruenitz and V. Srivatsan, journal OF Medicinal Chemistry 1992, 35, side 931-938.Andere Antiöstrogene with partial agonistischer effect or Östrogene with partial antagonistic component, like z. B. described in the essay ?Comparative Affinity OF Sterodial and Nonsterodial Antioestrogens, Cholesterol of derivative and Compounds with A Dialkylamino simmers chain for the advice of live Antioestrogen being thing Site? Biochemical Pharmacology, volume, 43, NO 12, pp. 2511-2518, 1992. , C.D.M.A. van the Koedijk, C. vis van Heemst, G.M. Elsendoorn, J.H.H. Thijssen and M.A. Have bright stone the Droloxifene similar or comparable characteristics, impacts and indications.

▲ top

The effectiveness the indications intended by Droloxifen for resulted in the bioassay, which was accomplished at rats. The test results are clarified by the following tables.

A 13wöchiger feeding attempt with Droloxifene Citrat at male and female rats was accomplished. Beside a control's group (?C? received the solvent from Droloxifene) six groups of treatments with the following dosages were examined:
< tb> < TABLE> Columns=2>
< tb> Group
< tb> Group of II: < SEP> 4 mg/kg body weight on the day
< tb> Group of III: < SEP> 8 mg/kg body weight on the day
< tb> Group of IV: < SEP> 16 mg/kg body weight on the day
< tb> Group of V: < SEP> 30 mg/kg body weight on the day
< tb> Group of VI: < SEP> 60 mg/kg body weight on the day
< tb> < /TABLE>

The following blood parameters were determined 6 and/or 13 weeks according to beginning of attempt: 1. Cholesterin 2. Triglyceride.

The following results were determined: All groups of treatments showed a clear lowering of the Cholesterinwerte.

The higher groups of doses showed beyond that significantly smaller Triglyceridspiegel; the fat mirror in the blood could be thus substantially lowered.

Cholesterin (mmol/l)

Male
EMI6.1

Female
[????.1]

Triglyceride (mmol/l)

Male
EMI8.1

Female
EMI9.1

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Claims of DE4401554	Print	Copy	Contact Us	Close

Result Page

1. Preparation to the therapy and prophylaxis characterized by illnesses, which arise with Imbalancen of Plasmalipiden, by the fact that as active substance a dose Droloxifene is contained

2. Preparation according to requirement 1, by the fact characterized that an indication is intended as Lipidsenker.

3. Preparation according to requirement 1, by the fact characterized that an indication is intended as Cholesterinsenker.

4. Preparation according to requirement 1, by the fact characterized that an indication is intended as Triglyceridsenker.

5. Preparation according to requirement 1, by the fact characterized that an indication is intended for the treatment of the Atherosklerose.

6. Preparation according to requirement 1, by the fact characterized that an indication is intended as Kardioprotektivum for the treatment of the Atherosklerose and.

7.Präparat according to requirement 1, by the fact characterized that an indication is intended as countersinks of the mixed Hyperlipoproteinämie.

8. Preparation according to requirement 1, by the fact characterized that an indication is intended as countersinks of complex Lipiden (Lipoiden), in particular of Phospholipiden or Glykolipiden.

9. Preparation after one of the requirements 1 to 8, by the fact characterized that a derivative derived from Droloxifene is contained.

10. Preparation after one of the requirements 1 to 9, by the fact characterized that Droloxifene Zitrat is contained.

11. Preparation after one of the requirements 1 to 10, by the fact characterized that Droloxifene is present as salt of inorganic acids.

12. Preparation after one of the requirements 1 to 10, by the fact characterized that Droloxifene is present as salt of organic acids.

13.Präparat after one of the requirements 1 to 12, by the fact characterized that the active substance is designed of Droloxifene as isomers form.

14. Preparation after one of the requirements 1 to 12, by the fact characterized that the active substance is designed of Droloxifene as enantiomere form.

15. Preparation after one of the requirements 1 to 12, by the fact characterized that the active substance is designed of Droloxifene as dia. stereoisomers form.

16. Preparation after one of the requirements 1 to 12, by the fact characterized that Droloxifene is designed as pharmaceutical compatible salt.

▲ top

17. Preparation after one of the requirements 1 to 16, by the fact characterized that the dose is trained as filling of a cap.

18. Preparation according to requirement 17, by the fact characterized that the filling is designed as a powdered substance.

19. Preparation according to requirement 17, by the fact characterized that the filling is designed as a substance dispersion.

20. Preparation after one of the requirements 1 to 16, by the fact characterized that the dose is arranged in the range of a tablet.

21. Preparation after one of the requirements 1 to 16, by the fact characterized that the dose is solved in a liquid to be dosed.

22. Preparation after one of the requirements 1 to 16, by the fact characterized that the dose is dispersed in a liquid.

23. Preparation after one of the requirements 1 to 22, by the fact characterized that the dose is arranged in a special galenischen formulation with retarded active substance release and/or extended retention.